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(54) Title: USE OF DEXTROMETHORPHAN OR DEXTRORPHAN FOR THE TREATMENT OF URINARY INCONTINENCE

(57) Abstract

Urinary incontenence is alleviated in a mammal by administering to the mammal a urinary incontinence alleviating amount of dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts, alone or in combination with a pharmacologically active agent such as an anticholinergic, sympathomimetic, tricyclic antidepressant, antispasmodic, direct-acting smooth muscle relaxant, estrogen, compound having estrogen-like activity, or any combination of the foregoing.

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MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
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RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
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USE OF DEXTROMETHORPHAN OR DEXTRORPHAN FOR THE TREATMENT OF URINARY INCONTINENCE

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to a method for treating urinary incontinence.

2. Description of Related Art

Urinary incontinence is a fairly common medical problem in which urine is involuntarily lost. Urinary incontinence may be transient or persistent. Common causes of transient urinary incontinence include infection, atrophic urethritis, administration of diuretics and delirium. Persistent urinary incontinence is classified into four types: (1) stress incontinence which involves involuntary loss of urine during coughing, sneezing, laughing, or other physical activity; (2) urge incontinence which involves involuntary loss of urine associated with an abrupt or strong desire to void; (3) overflow incontinence which involves involuntary loss of urine associated with over-distension of the bladder; and (4) mixed incontinence which involves a combination of at least two of the above types.

Persistent urinary incontinence can result from spastic or hyperactive bladder smooth muscle such as detrusor originating incontinence. In certain instances such incontinence is caused by loss of control resulting from spinal injury, parkinsonism, multiple sclerosis or recurrent bladder infection to name a few. Treatment of incontinence may involve surgery or administration of any of various pharmacological agents, e.g., a anticholinergic such as oxybutynin, atropine, propantheline, terodiline, dicyclomine and others, a sympathomimetic such as

ephedrine, pseudoephedrine, phenylpropanolamine and others, a tricyclic antidepressant such as amitriptyline, imipramine, doxepin and others, an estrogen or a direct acting antispasmodic such as flavoxate. In addition to treating incontinence, such pharmacological agents may cause other powerful physiologic responses such as excitability (sympathomimetics), and dry mouth, drowsiness, dizziness or hallucinations (anticholinergics or tricyclic antidepressants).

Other compounds described as useful for treating urinary incontinence are described, e.g., in U.S. Patent Nos. 4,645,758, 4,865,843, 5,080,905, 5,236,956, 5,233,053, 5,252,589, 5,258,390, 5,272,163, 5,340,805, 5,340,819, 5,340,826, and 5,266,596. U.S. Patent No. 5,192,751 describes the use of certain competitive N-methyl-D-aspartate (NMDA) receptor antagonists in the treatment of urinary incontinence. It is noted therein that a non-competitive NMDA receptor antagonist, MK-801, has been reported to produce an increase in frequency in micturition (Vera et al., Neurosci. Lett., 134, 135-138 (1991)).

Dextromethorphan and its main metabolite, dextrorphan, are non-competitive NMDA receptor antagonists having few, if any, side effects at indicated dosage levels. Dextromethorphan and dextrorphan have been used as antitussives, for treatment of chronic pain (U.S. Patent No. 5,352,683) and for inhibiting the development of tolerance to and/or dependence on a narcotic analgesic (U.S. Patent No. 5,321,012). Surprisingly, it has now been found that the non-competitive NMDA receptor antagonists dextromethorphan and dextrorphan are useful in the treatment of urinary incontinence.

SUMMARY OF THE INVENTION

In accordance with the present invention, there is provided a method for the treatment of urinary incontinence which comprises administering to a mammal exhibiting urinary incontinence a urinary incontinence alleviating amount of at least one morphinan selected from the group consisting of dextromethorphan, dextrorphan and pharmaceutically acceptable salts thereof. The method can optionally include administration of one or more pharmacologically active agents selected from the group consisting of anticholinergics, sympathomimetics, tricyclic antidepressants, antispasmodics, direct acting bladder smooth muscle relaxants, estrogens, compounds having estrogen-like activity, and any combination of the foregoing.

In another embodiment of the present invention, there is provided a method of decreasing micturition frequency in a mammal which comprises administering to a mammal a micturition decreasing amount of at least one morphinan selected from the group consisting of dextromethorphan, dextrorphan and pharmaceutically acceptable salts thereof. The method can optionally include administration of any of the pharmacologically active agents mentioned above.

BRIEF DESCRIPTION OF THE DRAWINGS

In the accompanying drawings:

Fig. 1 is a graphical representation of test results showing therapeutic effects of intravenous administration of dextromethorphan on absolute micturition pressures in rats; and,

Fig. 2 is a graphical representation of test results showing therapeutic effects of intravenous administration of dextromethorphan on micturition frequency in rats.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Dextromethorphan ((+)-3-methoxy-N-methylmorphinan) and dextrorphan ((+)-3-hydroxy-N-methylmorphinan), their mixtures and pharmaceutically acceptable salts are utilized in accordance with the method of the present invention. Accordingly, dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts are administered by any known route of administration for the relief of symptoms of bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder such as urgency, frequency, urine leakage, urge incontinence, stress incontinence, overflow incontinence, mixed incontinence or dysuria. Dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts are also useful in the treatment of interstitial cystitis, a chronic inflammatory condition of unknown etiology resulting in reduced bladder capacity and severe bladder irritative symptoms. Administration of dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts acts to quiet the bladder and reduce the frequency of micturition.

Administration of dextromethorphan, dextrorphan their mixtures and/or pharmaceutically acceptable salts can be orally or transdermally or by intravenous, intramuscular, subcutaneous, intrathecal, epidural or intracerebro-ventricular injection. Effective dosage levels can vary widely, e.g., from about 0.25 to about 250 mg/day, but actual amounts will, of course, depend on the

state and circumstances of the patient being treated. As those skilled in the art recognize, many factors that modify the action of the active substance herein will be taken into account by the treating physician such as the age, body weight, sex, diet and condition of the patient, the time of administration, the rate and route of administration, and so forth. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage determination tests in view of the experimental data provided herein.

Therapeutic compositions containing dextromethorphan, dextrorphan, their mixtures and/cr pharmaceutically acceptable salts will ordinarily be formulated with one or more pharmaceutically acceptable ingredients in accordance with known and established practice. Thus, dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts can be formulated as a liquid, powder, elixir, injectable solution, etc. Formulations for oral use can be provided as hard gelatin capsules wherein dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts are mixed with an inert solid diluent such as calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts are mixed with an oleaginous medium, e.g., liquid paraffin or olive oil.

Aqueous suspensions can contain the dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts in admixture with pharmaceutically acceptable excipients such as suspending agents, e.g., sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum

acacia; dispersing or wetting agents such as naturally occurring phosphatide, e.g., lecithin, or condensation products of an alkaline oxide with fatty acids, e.g., polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, e.g, heptadecaethylene-oxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, e.g., polyoxyethylene sorbitol monoleate or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, e.g., polyoxyethylene sorbitan monoleate. Such aqueous suspensions can also contain one or more preservatives, e.g., ethyl-or-n-propyl-p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin or sodium or calcium cyclamate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, e.g., sweetening, flavoring and coloring agents, can also be present. Syrups and elixirs can be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations can also contain a demulcent, a preservative and flavoring and coloring agents.

Dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts are advantageously provided in sustained release dosage form of which many kinds are known, e.g., as described in U.S. Patent Nos. 4,788,055; 4,816,264; 4,828,836; 4,834,965; 4,834,985;

4,996,047; 5,071,646; and, 5,133,974, the contents of which are incorporated by reference herein.

It is also within the scope of this invention to administer dextromethorphan, dextrorphan, their mixtures and/or pharmaceutically acceptable salts prior to, concurrently with, or after administration of any other known pharmacologically active agent useful for treating urinary incontinence. Such agents include, but are not limited to, anticholinergics such as oxybutynin, atropine, propantheline, terodiline, dicyclomine, etc., sympathomimetics such as ephedrine, pseudoephedrine, epinephrine, phenylpropanolamine, etc., tricyclic antidepressants such as imipramine, doxepin, amitriptyline, etc., estrogens or estrogen-related compounds having estrogen-like activity such as estradiol, estrone, etc., and antispasmodics or direct acting bladder smooth muscle relaxants such as flavoxate. For a detailed discussion of these pharmacologically active agents, reference may be made to "Goodman and Gillman's Pharmacological Basis of Therapeutics", Goodman et al., eds. 7th ed., 1985, Macmillan and Company, New York.

The examples that follow are illustrative of the present invention and should not be construed as limiting.

EXAMPLE 1

Ten female Sprague-Dawley rats having a mean weight of 263 ± 19 g were anesthetized with urethane (1.2 g/k, sc.). A midline incision was performed to expose the bladder and a 23G catheter was inserted into the bladder dome for the measurement of intravesical pressure. A non-stop transvesical cystometrogram, as described in J. Pharmacological. Methods, 15, pp. 157-167 (1986), was used, at a filling rate of 0.216 ml/min. of saline, to access the filling and voiding characteristics of the

bladder. Through the continuous cystometry method thus afforded, consecutive micturition could be recorded. Dextromethorphan was given at intravenous does of: 1.0, 3.0, 10, 30, 50 mg/kg after the initial baseline micturition sequence was reliably measured for approximately 12 min. From these recordings the absolute values in maximum pressure obtained and the frequency of micturition was measured. A dose response curve illustrating the effect of dextromethorphan on the absolute micturition pressures in the range of 1-50 mg/kg is given in Fig. 1. Data given are mean and SE.

The volume evoked micturition reflex was suppressed in a dose sensitive manner as seen from the effect of increasing doses of dextromethorphan on the cystometrogram. In particular it was found that at doses in the range of 10-30 mg/kg, the volume evoked micturition contractions are almost totally suppressed. A significant sustained reduction in detrusor pressure is produced at a dose level of 3 mg/kg and a 50% reduction is evident at 10 mg/kg. As shown in Fig. 1, at higher doses of dextromethorphan, the rate of decrease in detrusor pressure is diminished. Furthermore at does higher than 10 mg/kg the effect of the drug appears to be bimodal, producing an initial increase in detrusor pressure before suppression.

The corresponding dose response effect of dextromethorphan on the frequency of micturition is given in Fig. 2. As shown, the frequency of micturition decrements gradually with respect to dose when compared to the pressure.

EXAMPLE 2

A capsule containing dextromethorphan hydrobromide contains the following ingredients:

Ingredient	mg/Capsule
Dextromethorphan Hydrobromide USP	20
Pregelatinized Starch NF	50
Colloidal Silicon Dioxide	1.5

EXAMPLE 3

A tablet containing dextromethorphan hydrobromide contains the following ingredients:

Ingredient	mg/Tablet
Dextromethorphan Hydrobromide USP	20
Microcrystalline Cellulose NF	17
Lactose NF anhydrous	68
Croscarmellose NF	1
Colloidal Silicon Dioxide	1.5
Magnesium Stearate NF	1.5

EXAMPLE 4

A controlled release tablet containing dextromethorphan hydrobromide contains the following ingredients:

Ingredient	mg/Tablet
Dextromethorphan Hydrobromide USP	40
Lactose NF	70
Methocel E 15LV	100
Ethylcellulose NF	35
Magnesium Stearate NF	15
Colloidal Silicon Dioxide NF	2

The embodiments and examples given above are illustrative of the present invention. Consequently it should be understood that modifications can be made by those with ordinary skill in the art that are intended to be covered by the following claims.

WHAT IS CLAIMED IS:

1. A method of treating urinary incontinence which comprises administering to a mammal exhibiting urinary incontinence a urinary incontinence alleviating amount of at least one morphinan selected from the group consisting of dextromethorphan, dextrorphan and pharmaceutically acceptable salts thereof.

2. The method of Claim 1 wherein the morphinan is contained in a pharmaceutically acceptable vehicle.

3. The method of Claim 1 therein the morphinan is provided in sustained release dosage form.

4. The method of Claim 1 wherein the morphinan is administered orally, intravenously, intramuscularly, subcutaneously, transdermally or intrathecally.

5. The method of Claim 1 which further comprises administering a pharmacologically active agent selected from the group consisting of anticholinergic, sympathomimetics, tricyclic antidepressants, antispasmodics, direct-acting bladder smooth muscle relaxants, estrogens, compounds having estrogen-like activity, and any combination of the foregoing.

6. The method of Claim 5 wherein the pharmacologically active agent is selected from the group consisting of oxybutynin, atropine, propantheline, terodiline, dicyclomine, ephedrine, pseudoephedrine, phenylpropanolamine, amitriptyline, imipramine, doxepin, an estrogen and flavoxate.

7. The method of Claim 5 wherein the morphinan is administered concurrently with the pharmacologically active agent.

8. The method of Claim 7 wherein the morphinan and pharmacologically active agent are contained in a pharmaceutically acceptable vehicle.

9. The method of Claim 5 wherein the morphinan and pharmacologically active agent are provided in sustained release dosage form.

10. The method of Claim 5 wherein the morphinan and the pharmacologically active agent are administered orally, intravenously, intramuscularly, subcutaneously, transdermally or intrathecally.

11. A method of decreasing micturition frequency in a mammal which comprises administering to a mammal a micturition decreasing amount of a morphinan selected from the group consisting of dextromethorphan, dextrorphan and pharmaceutically acceptable salts thereof.

12. The method of Claim 11 wherein the morphinan is contained in a pharmaceutically acceptable vehicle.

13. The method of Claim 11 therein the morphinan provided is provided in sustained release dosage form.

14. The method of Claim 11 wherein the morphinan is administered orally, intravenously, intramuscularly, subcutaneously, transdermally or intrathecally.

15. The method of Claim 11 which further comprises administering a pharmacologically active agent selected from the group consisting of anticholinergic, sympathomimetics, tricyclic antidepressants, antispasmodics, direct-acting bladder smooth muscle relaxants, estrogens, compounds having estrogen-like activity estrogen, and any combination of the foregoing.

16. The method of claim 15 wherein the pharmacologically active agent is selected from the group consisting of oxybutynin, atropine, propantheline, terodiline, dicyclomine, ephedrine, pseudoephedrine, phenylpropanolamine, amitriptyline, imipramine, doxepin, an estrogen and flavoxate.

17. The method of Claim 15 wherein the morphinan is administered concurrently with the pharmacologically active agent.

18. The method of Claim 17 wherein the morphinan and pharmacologically active agent are contained in a pharmaceutically acceptable vehicle.

19. The method of Claim 15 wherein the morphinan and pharmacologically active agent are provided in sustained release dosage form.

20. The method of Claim 15 wherein the morphinan and the pharmacologically active agent are administered orally, intravenously, intramuscularly, subcutaneously, transdermally or intrathecally.

21. A method of treating interstitial cystitis which comprises administering to a mammal exhibiting interstitial cystitis an effective amount of a morphinan selected from the group consisting of dextromethorphan, dextrorphan and pharmaceutically acceptable salts thereof.

22. The method of Claim 21 which further comprises administering a pharmacologically active agent selected from the group consisting of anticholinergics, sympathomimetics, tricyclic antidepressants, antispasmodics, direct-acting bladder smooth muscle relaxants, estrogens, compounds having estrogen-like activity, and any combination of the foregoing.

23. The method of Claim 22 wherein the pharmacologically active agent is selected from the group consisting of oxybutynin, atropine, propantheline, terodiline, dicyclomine, ephedrine, pseudoephedrine, phenylpropanolamine, amitriptyline, imipramine, doxepin, estrogens and flavoxate.

24. A composition comprising at least one morphinan selected from the group consisting of dextromethorphan, dextrorphan and the pharmaceutically acceptable salts thereof and at least one pharmacologically active agent selected from the group consisting of anticholinergics, sympathomimetics, tricyclic antidepressants, antispasmodics, direct-acting bladder smooth muscle relaxants, estrogens, compounds having estrogen-like activity, and any combination of the foregoing.

25. The composition of Claim 24 wherein the pharmacologically active agent is selected from the group consisting of oxybutynin, atropine, propantheline, terodiline, dicyclomine, ephedrine, pseudoephedrine, phenylpropanolamine, amitriptyline, imipramine, doxepin, estrogen an and flavoxate.

26. The composition of Claim 24 in sustained release dosage form.

27. The composition of Claim 25 in sustained release dosage form.

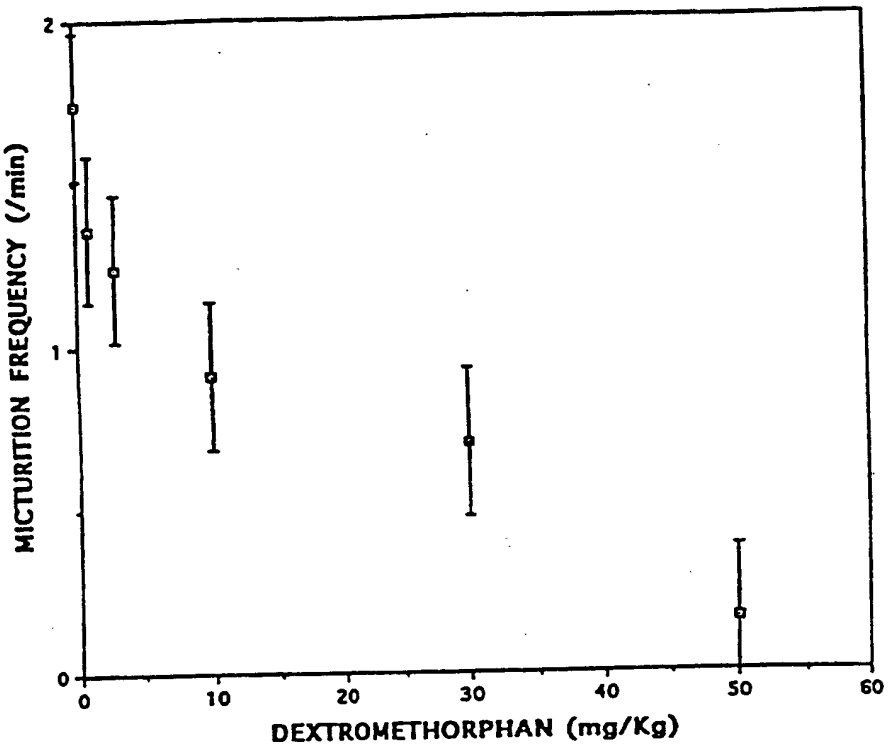
MICTURITION FREQUENCY (/min)
2
1
0
0
10
20
30
40
50
60
DEXTROMETHORPHAN (mg/Kg)

FIG.1

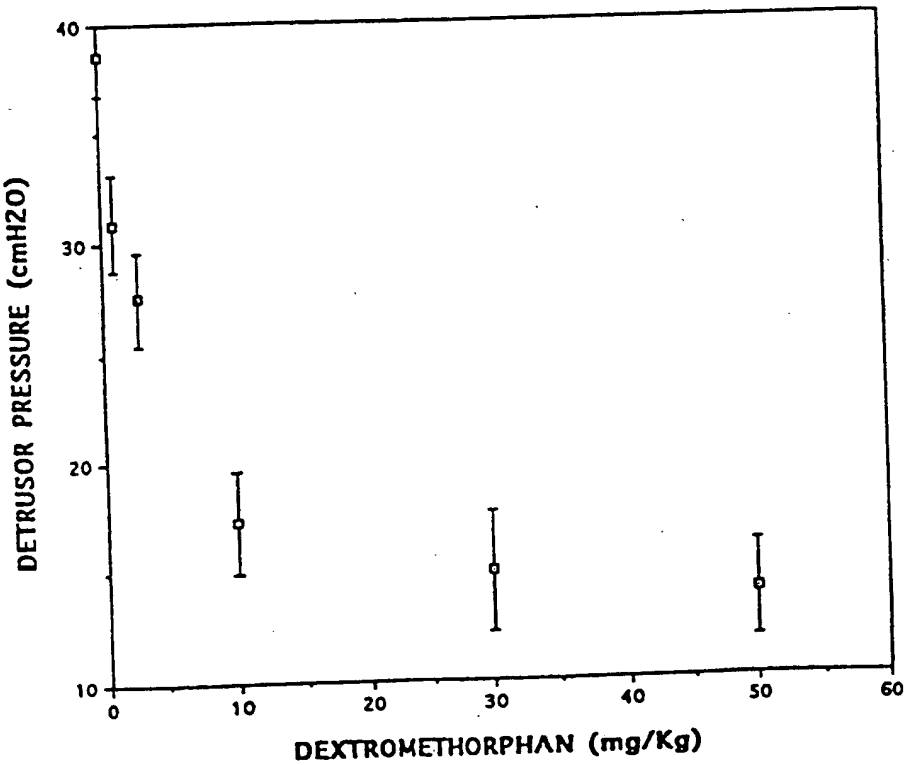
DETRUSOR PRESSURE (cmH2O)
40
30
20
10
0
10
20
30
40
50
60
DEXTROMETHORPHAN (mg/Kg)

FIG.2

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LV	Latvia
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MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/485 A61K35/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J PHARMACOL EXP THER, NOV 1984, 231 (2) P254-60, UNITED STATES, XP000600400 DRAY A ET AL: "Inhibition of urinary bladder contractions by a spinal action of morphine and other opioids." see the whole document especially abstract ---	1,2,4, 11,12, 14,21
X	BRAIN RES, 297 (1). 1984. 191-195., XP000600398 DRAY A ET AL: "MORPHINE AND THE CENTRALLY MEDIATED INHIBITION OF URINARY BLADDER MOTILITY IN THE RAT" see the whole document especially abstract ---	1,2,4, 11,12, 14,21

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 1996	17. 10. 96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Mair, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EUR J PHARMACOL, 98 (1). 1984. 155-156., XP000600399 DRAY A ET AL: "OPIOIDS AND CENTRAL INHIBITION OF URINARY BLADDER MOTILITY" see the whole document especially page 155, righthand column, line 12	1,2,4, 11,12, 14,21
X	NEUROSCIENCE LETTERS, vol. 126, no. 2, 1991, pages 141-144, XP000600387 YOSHIYAMA, M. ET AL: "The effects of MK-801, an NMDA receptor antagonist, on the micturition reflex in the rat" see the whole document especially page 143, righthand column, line 8-13	1-27
X	EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 181, 1990, pages 105-109, XP000600388 MAGGI, C.A. ET AL: "The effect of MK-801 on the micturition reflex in anesthetized rats" see the whole document especially page 108, lefthand column, line 44-righthand column, line 3	1-27
X	PAIN, vol. 57, no. 3, 1994, pages 335-340, XP000600392 RICE, A.S.C ET AL: "Pre-emptive intrathecal administration of an NMDA receptor antagonist (AP-5) prevents hyper-reflexia in a model of persistent visceral pain" see the whole document especially page 340, lefthand column, line 7-19	1-27

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/US 96/ 02809

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1 - 23 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.